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Late effects in adult survivors of childhood cancer: the need for life-long follow-up

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Background: To assess health status and health-related quality of life (HRQoL) in childhood cancer survivors who were not involved in regular long-term follow-up.

Patients and methods: One hundred and twenty-three long-term survivors, median age 33 (19–50) years, follow-up 27 (9–38) years, were recalled to the long-term follow-up clinic. Most of them were treated in the period 1970–1990. Late effects were graded using the Common Terminology Criteria for Adverse Events, version 3 (CTCAEv3). HRQoL was assessed by RAND-36. Socio-economic factors were compared with data from Statistics Netherlands (CBS).

Results: Grade 1–2 late effects were found in 54% of the survivors, grade 3–4 in 39%, two or more late effects in 70% and grade 2–4 previously unknown late effects in 33%. Survivors had significantly lower scores on RAND-36 compared with controls.

Conclusions: As nearly 40% of these long-term childhood cancer survivors suffer from moderate to severe late effects and 33% had previously unknown late effects it is worthwhile recalling these patients to follow-up. Where and by whom this follow-up can best be done is still a question that needs to be answered.

Key words: childhood cancer survivors, grading of late effects, long-term follow-up, HRQoL

introduction

As a result of improved survival of childhood cancer there is a growing population of long-term survivors [1]. This ever enlarging population of young adult childhood cancer survivors is at increased risk of considerable morbidity and even mortality as a result of late adverse effects of their previous treatment.

Adverse late effects secondary to previous treatment with chemotherapy or radiation are common; as many as two-thirds of survivors of childhood cancer will experience such late effects [2–5]. All organ systems are at risk, with late effects including cognitive impairment, infertility, alterations in growth and development, organ system damage and second malignancies [6, 7]. To ensure that survivors enjoy the best possible quantity and quality of life it is important to recognize and treat adverse effects if possible at an early stage [7]. Most clinicians advocate that childhood cancer survivors should be followed for life [8, 9]. However, at present not all long-term survivors participate in long-term follow-up. Many were discharged years ago and some doctors still discharge survivors as soon as they reach adulthood. From

an analysis performed by the Children's Cancer Survivors Study Group (CCSS) it appeared that only 31% of survivors who were 18–19 years of age at time of interview had been seen by a health-care provider at a paediatric cancer centre in the previous 2 years. This percentage steadily decreased with age of the survivor, to 17% of those who were 35 years or older [10]. These older survivors reach a period in life when many common chronic diseases begin to arise. In addition, certain cancer treatments in childhood may cause an earlier or more accelerated course of these diseases, such as cardiovascular disease, osteoporosis or second malignancy [11]. Considering the risk of adverse late effects of treatment our hospital set up a long-term follow-up (LTFU) clinic in 1995. Childhood cancer survivors made a transition from the regular paediatric oncology clinic to this LTFU clinic as soon as they had been off-treatment for 5 years. From 2004 we recalled adult survivors who in the past, mostly in the period 1970–1990, had been discharged from the paediatric oncology clinic, which in those days usually occurred if they had no evidence of disease for 5–10 years. Assessment of these adult survivors for possible adverse effects of treatment was done by a general practitioner (GP) employed by the paediatric oncology department and trained by the paediatric oncologists. The objective of this manuscript is to report the

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health status and health related quality of life (HRQoL) of all survivors seen in the first year by the GP.

methods

patients

Patients were eligible for recall to the LTFU clinic if they had been treated previously at the paediatric oncology department of the University Medical Center Groningen, The Netherlands, were at least 5 years off-treatment and were not yet involved in any childhood cancer follow-up in either the same hospital or elsewhere. One hundred and thirty-three out of 210 eligible patients were chosen at random and recalled to the LTFU clinic between May 2004 and May 2005. Ten of them (10%) refused for several reasons, most often because they did not want to look back but wanted to look forward and rebuild their life. The remaining 123 patients (66 males, 57 females) were seen by a doctor with special interest in late effects. According to their diagnosis and treatment in the past, the patients underwent risk-based evaluations such as hormonal assessments, echocardiography, bone mineral density tests or pulmonary function tests. Due to the fact that Dutch guidelines are still under development, we followed the guidelines according to the practice statement 'Therapy Based Long Term Follow Up' produced by the United Kingdom Children's Cancer Study Group (UKCCSG) Late Effects Group (LEG). In addition patients who had received chest irradiation and therefore were at risk for coronary disease underwent electron beam computed tomography (EBCT), which is a non-invasive test to detect calcium deposits in the coronary arteries. Coronary artery calcification is expressed as a calcification score, the standard method is described by Agatston *et al.* [12]. A total calcium score is determined by summing up the individual scores from each of the four coronary arteries. The scores are compared with the percentile ranks of Hoff *et al.* [13], which are adjusted for age and gender.

Patients were diagnosed with childhood cancer between 1968 and 1997. Patients with a central nervous system tumour were excluded because most of them were followed separately by a multidisciplinary neuro-oncology team. No significant differences were found in gender, diagnosis and age at diagnosis between the study group and the 87 patients who were not yet recalled. Characteristics of the participating patients are shown in Table 1.

Socio-economic factors of the study group were compared with an age-matched group in the Dutch population, analysed by Statistics Netherlands (CBS).

grading of late effects

Late effects were graded using the Common Terminology Criteria for Adverse Events, Version 3 (CTCAEv3), developed by the National Cancer Institute (NCI). The CTCAEv3 represents the first comprehensive, multimodality grading system to include both acute and late effects [14]. The CTCAEv3 grades adverse effects from 0 to 4. Grade 1 effects are minimal and usually asymptomatic. Grade 2 effects are moderate, are usually symptomatic but do not impair activities of daily living. Grade 3 effects are considered severe, requiring more serious interventions. Grade 4 effects are potentially life threatening. Low-grade events (grades 1 and 2) are considered tolerable and manageable and should be distinguished from severe or very undesirable high-grade events (grade 3 and 4).

health related quality of life

HRQoL was assessed by RAND-36, which is an internationally used valid and reliable generic self-report questionnaire. It contains eight different subscales: Physical Functioning (PF), Social Functioning (SF), Role limitations due to Physical problems (RP), Role limitations due to Emotional problems (RE), Mental Health (MH), Vitality (VT), Bodily Pain

Table 1. Demographic and clinical data of 123 participating adult survivors

	Study group (<i>n</i> = 123)	CBS
Patient characteristics		
Age at study (years) ^a	33 (19–50)	
Age at diagnosis (years) ^a	6 (0–20)	
Time since diagnosis ^a	27 (9–38)	
Male ^b	66 (53.7)	
Living with parents ^b	24 (19.5)*	9%
Living with a partner ^b	70 (56.9)	
Childless ^b	74 (60.2)*	50%
Type of cancer ^b		
Leukaemia	56 (45.5)	
Malignant lymphoma	21 (17.1)	
Bone tumour	19 (15.4)	
Soft tissue sarcoma	7 (5.7)	
Wilms' tumour	4 (3.3)	
Langerhans cell histiocytosis	8 (6.5)	
Other	8 (6.5)	
Treatment ^b		
Chemotherapy only	45 (36.6)	
Radiotherapy only	5 (4.1)	
Chemo- and radiotherapy	71 (57.7)	
Cranial radiation	55 (44.7)	
Surgery only	2 (1.6)	

^aMedian (range).

^bNumber (%).

**P* < 0.05.

CBS, Statistics Netherlands.

(BP) and General Health perception (GH). For each subscale, scores were coded, summed up and transformed to a scale from 0 (worst health) to 100 (best health) [15]. The questionnaire takes about 10 min to complete. The instrument has been translated into Dutch [16] and has been validated for the Dutch population [17]. RAND-36 has already been used in several other studies for assessment of HRQoL in childhood cancer survivors [18, 19]. Mean scores of the available Dutch norm group aged 25–44 years (*n* = 416) were used as reference values.

statistics

Data were analysed by descriptive techniques using frequencies, percentages, means and medians as appropriate. The one-sample *t*-test was used to compare the mean RAND scores of the study group with the mean scores of the Dutch control group. The one-sample *t*-test was also used to compare socio-economic variables of the study group with an age-matched control group from the Dutch population. Because of the small study population, differences between cancer types were not analysed. To investigate which variables predict survivors QoL, all significant characteristics identified from univariate analysis were studied with multiple linear regression analysis. A significance level of *P* < 0.05 was applied in all analyses.

results

Sixty-six out of 123 (54%) patients had a mild late effect (grade 1 or 2) and 48/123 (39%) had a moderate to severe late effect (grade 3 or 4) (Table 2). Almost 70% had two or more late effects. Forty-one out of 123 patients (33%) were diagnosed with a grade 2–4 late effect that was previously unknown and that required treatment or closer surveillance (Table 3). Five

Table 2. Late effects graded with Common Terminology Criteria for Adverse Events (CTCAE) version 3 in 123 survivors

Category	<i>n</i>	%
No late effect	9	7
Grade 1 or 2	66	54
Grade 3 or 4	48	39
Single late effect	29	24
Two or more late effects	85	69

Table 3. Previously undetected late effects that required therapy or closer surveillance in 123 survivors

Category	<i>n</i>	%
Second malignancy	5	4%
Growth hormone deficiency	8	6%
Osteoporosis	7	6%
Arthrosis hip (osteonecrosis)	2	2%
Cardiac problem	10	8%
Reproductive problem	7	5%
Hepatitis C	1	1%
Thyroid problem	1	1%
Total	41	33%

survivors had a second malignant tumour (meningioma, oesophageal carcinoma and three basocellular carcinomas) that had not been recognized before and eight patients had a previously unknown growth hormone deficiency. Seven patients, four with Hodgkin's lymphoma, two with non-Hodgkin's lymphoma and one with a rhabdomyosarcoma, who had been treated with chest radiation, underwent electron beam tomography because they were at risk for coronary artery disease. All of them had Agatston scores >90th percentile ranks of Hoff et al. [13] and three (43%) had Agatston scores >400. These patients were referred to the cardiologist for further cardiac evaluation (Table 3). Patients treated with a combination of chemo- and radiotherapy had significantly ($P < 0.001$) more moderate to severe late effects compared with patients treated with chemotherapy alone.

Survivors lived significantly more often with their parents than an age-matched group from the Dutch population (19.5% vs. 9%, $P = 0.004$) and were more often childless (60.2% vs. 50%, $P = 0.024$) (Table 1).

The RAND-36 was sent to all 123 participating survivors before they visited the LTFU clinic, and was returned by 121 (98%) of them. The outcomes on the various subscales of the RAND-36 for the study group and the Dutch control group are shown in Table 4. Survivors showed lower HRQoL scores in comparison to the control group on the subscales PF ($P = 0.033$), SF ($P = 0.009$), VT ($P = 0.003$) and GH ($P = 0.000$). Survivors who had no late effects, or only mild late effects, have significantly better scores on the RAND subscales PF ($P = 0.023$, $P = 0.011$), RP ($P = 0.030$, $P = 0.044$), VT ($P = 0.009$) and GH ($P = 0.003$) than survivors who had severe late effects. Survivors with a job had significant better scores on the RAND subscales PF ($P = 0.019$) and GH ($P = 0.017$).

Table 4. Means and standard deviations for the RAND-36 subscales, in 123 survivors and in Dutch controls (25–44 years)

	Study group (<i>n</i> = 123)		Controls (<i>n</i> = 416)	
	Mean	SD	Mean	SD
PF	85.9**	19.2	89.7	16.3
SF	84.7**	19.5	89.4	17.0
RP	79.5	32.5	82.7	32.2
RE	87.5	28.7	84.6	31.5
MH	77.2	15.9	77.9	17.7
VT	62.7**	20.1	68.2	18.9
BP	83.8	19.5	84.0	22.9
GH	67.2***	22.6	75.9	20.2

** $P < 0.01$: survivors versus controls.

*** $P < 0.001$: survivors versus controls.

SD, standard deviation; PF, physical functioning; SF, social functioning; RP, role limitations due to physical problems; RE, role limitations due to emotional problems; MH, mental health; VT, vitality; BP, bodily pain; GH, general health perceptions.

Living with a partner was related to higher scores on the subscales RE ($P = 0.027$) and MH ($P = 0.003$).

Patients who received cranial radiation had unexpectedly significant better scores on the RAND subscales GH and BP compared with those who had not received cranial radiation.

discussion

This study shows that a substantial number (39%) of survivors who were treated in the period 1970–1990 have moderate to severe late effects with significantly lower quality of life as expressed by scores on the RAND-36 and compared with survivors who have no or only mild late effects. Thirty-three per cent of these late effects were previously unknown and required treatment or closer surveillance. Some of these late effects, such as a meningioma, were diagnosed following specific complaints and symptoms that were reported at the long-term follow-up clinic and that had failed to be appreciated until then. This suggests that education of patients as well as physicians who might be involved in follow-up care of these survivors is an important issue. Our results support the importance of life-long follow-up by physicians with knowledge of late effects. In addition more strategies have to be developed to improve the knowledge of childhood cancer survivors and non-specialist clinicians, such as for example the UKCCSG's 'After cure package'. Research will continue to have an important role in LTFU to develop reduced treatment strategies for treatment of the primary disease, like reduced doses of radiation and chemotherapy, less toxic chemotherapy and addition of cardioprotectants, which can maintain high cure rates with less late toxicity.

Detection and treatment of problems that would otherwise be neglected or detected much later may improve patients' future quality of life. The data from the current study confirm the findings of other studies that a significant proportion of childhood cancer survivors have moderate to severe late effects that require treatment, and affect their HRQoL [2, 20].

However, the percentages in our study are even higher than those found by others who found approximately 30% patients with moderate to severe late effects (versus 39% in our study) and approximately 40% with two or more late effects (versus 70% in ours) [2–4, 20]. Most research has focused on the late effects during the first 10–15 years after therapy. In our study time since diagnosis was longer than 20 years, which is longer than in most other studies. In an earlier study we showed that the prevalence and the severity of late effects increased with time since diagnosis [21]. As time since diagnosis extends, medical problems associated with aging may exhibit an earlier onset or more accelerated course following certain cancer therapies. Oeffinger [11] described that cancer survivors, diagnosed with cancer between 1970 and 1986, were more vulnerable to diseases that are associated with aging, like second cancers, heart conditions, kidney disease, musculoskeletal problems, osteoporosis and sterility compared with their siblings. The incidence of chronic conditions increases over time and does not appear to plateau. Survivors lived significantly more often with their parents and were more often childless than an age-matched group from the Dutch population. Other studies confirm these findings and they also find that a lower percentage of survivors than peers are in employment [22, 23], which we did not include in our study.

In our study, survivors who did not have a partner had a lower quality of life, expressed as lower scores on the physical functioning and general health perception subscales of the RAND-36 and those without a job had lower scores on the role limitations due to emotional problems and mental health subscales. This might be explained by the fact that these survivors lack emotional support from a partner and are likely to have lower incomes. In the CCSS studies survivors with low household income were at risk for adverse health status [23]. Several limitations can be recognized in the interpretation of the current study. The sample size was relatively small, limiting analysis between cancer types or different treatment modalities. Patients with CNS tumours were not included. This might have caused an underestimation of late effects and an overestimation of HRQoL, as these survivors generally exhibit more severe treatment sequelae [19, 23, 24]. Quality of life was measured by RAND-36, which is a generic outcome measure focusing on HRQoL. RAND-36 has been used in several other studies to determine HRQoL in adult childhood cancer survivors [18, 19]. Specific questionnaires would probably be better to measure the functioning of survivors, but validated questionnaires designed for childhood cancer survivors in particular are hardly available. Finally, some patients, especially those with cognitive defects following cranial irradiation, were not able to complete the RAND-36 correctly and needed help from family members. This might have influenced the outcome. One could speculate that family members are probably positively biased with regard to their kin's quality of life. Apparently the RAND-36, as a self-report questionnaire, is less suitable for patients with impaired cognitive functions. This could be an explanation for our finding that survivors treated with cranial radiation had higher scores on the subscales bodily pain and general health perception.

This study supports the fact that the growing population of aging childhood cancer survivors can be viewed as a high-risk population for an impaired health status and HRQoL and supports the necessity of life-long follow-up.

conflict of interest statement

None declared.

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